Management of Locally Advanced Rectal Adenocarcinoma

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INTRODUCTION

Colorectal cancers are among the most common cancers worldwide, and there is a high mortality rate for advanced-stage disease. Approximately 132,000 new cases of colorectal cancer will be diagnosed in the United States in 2015, and approximately 40,000 of these cases will be primary rectal cancers.1 The incidence and mortality rates have been steadily declining over the past two decades, largely through advances in screening and improvements in treatment.2,3 However, rectal cancer remains a significant cause of morbidity and mortality in the United States and worldwide.

The worldwide incidence rates of colorectal cancers are variable, with the highest rates of disease in North America, Europe, and Australia, and the lowest rates in Africa and parts of Asia.4 Within a population, risk factors for the development of disease include lower socioeconomic status. This has been attributed to decreased physical activity, obesity, smoking, decreased dietary intake of fruits and vegetables, as well as decreased adherence to screening guidelines in persons of lower socioeconomic status.5–8

The majority of colorectal cancers occur sporadically and incidence increases with age, especially after the fourth decade of life. The incidence in the older population is decreasing while incidence rates in patients under 50 years of age have been increasing, but most new cases are still diagnosed in older patients.9 Though relatively rare, hereditary cancer syndromes dramatically increase the risk of colorectal cancers in affected individuals. The most common inherited cause of colorectal cancer is the autosomal dominant hereditary nonpolyposis colorectal cancer (HNPCC), or Lynch syndrome. Less common inherited colorectal cancer syndromes include familial adenomatous polyposis and its variants (Gardner and Turcot syndromes) and MUTYH-associated polyposis. A unique set of screening guidelines for both colorectal and noncolorectal cancers are warranted for patients identified with these syndromes.10–12

Inflammation has long been thought to play a role in colorectal carcinogenesis. Patients with chronic bowel inflammation from ulcerative colitis
and Crohn’s disease have a higher risk of cancer development, as do patients with a history of radiation. These patients should also be screened more frequently than the general population.\textsuperscript{13–15} Because they decrease inflammation, aspirin and nonsteroidal anti-inflammatory drugs have long been evaluated as a protective factor against colorectal cancer development. A significant number of observational and randomized trials have shown a reduction in both the incidence of colorectal adenomas and colorectal cancers.\textsuperscript{16–18} However, because of their side effects these drugs are not yet recommended for the general population, although they are suggested for select high-risk patients, such as those with Lynch syndrome.\textsuperscript{19}

This review focuses on the diagnosis, management, and surveillance of locally advanced rectal cancer. Although often grouped with colon cancers, rectal cancers differ from colon cancers in terms of diagnosis and management. Though early-stage disease can be cured with local excision, most cancers are more advanced at presentation in terms of depth of tumor invasion and adherence to local pelvic structures. Because of surgical challenges regarding tumor location, rectal cancers have historically been at higher risk for local recurrence than colon cancers. In addition, managing rectal tumors requires particular attention to quality of life issues, such as anal sphincter preservation and the bowel toxicity and sexual dysfunction that can arise from radiation. For the best outcome, these cancers require a multidisciplinary approach including chemotherapy, radiation, and surgery.

**CLINICAL EVALUATION AND STAGING**

**CASE PATIENT**

A 64-year-old woman without significant past medical or family history presents to her primary care physician after noting red blood in the toilet and pain with defecation for the last 3 weeks. She reports no abdominal or pelvic pain. Physical exam is notable for no palpable inguinal lymph nodes and no external anal lesions or hemorrhoids. Rectal exam reveals a palpable mass at 9 o’clock and stool guaiac test is positive. Laboratory evaluation is notable for hemoglobin of 10 mg/dL and a mean corpuscular volume of 75 fL. Rigid sigmoidoscopy reveals a nonobstructing ulcerated mass 4 cm from the anal verge. Biopsy is performed and findings are consistent with grade II adenocarcinoma.

• How is rectal cancer defined?

On average, the human rectum is 12 cm long. The sigmoid colon becomes the rectum at the fusion of the sigmoid colon tenia. The distal end of the rectum transitions to an ampulla with a circumference of 35 cm rather than the 15 cm of the rest of the rectum. The end of the rectum is considered to be the puborectalis ring or the dentate line, where the transitional mucosa of the anus begins.\textsuperscript{20} The majority of the rectum (10 cm) lies outside the peritoneum, demarcated by the peritoneal reflection.

The significant majority of rectal cancers are carcinomas, which are primarily comprised of adenocarcinomas. Though squamous cell carcinomas, adenosquamous carcinomas, and undifferentiated carcinomas have been described, they are relatively unusual. Rarely, other tumors of the rectum, including neuroendocrine tumors, hamartomas, and lymphomas, have been described.\textsuperscript{21} After establishing the histology of the tumor, the grade of differentiation is described. This is based on the degree of gland formation present, with well and moderately differentiated tumors exhibiting defined glandular structures and poorly differentiated tumors not exhibiting defined structures. The tumor
grade has been evaluated and is generally found to have prognostic significance.22

• What pretreatment staging evaluation is recommended?

Even though screening for colorectal cancer is increasingly utilized, the majority of patients are still diagnosed after presenting due to symptoms. Careful medical history should include information about constitutional symptoms like weight loss and fatigue as well as local issues such as pain or changes in urinary and bowel habits. Particular attention should be paid to symptoms of potential obstruction, which might warrant urgent surgical intervention. Physical exam should include rectal exam and stool guaiac assessment. Basic blood testing should be performed to evaluate for significant anemia and abnormal liver function tests and generally includes a complete blood count, chemistry panel, liver function tests, and measurement of carcinoembryonic antigen (CEA). Though CEA is not indicated for screening or diagnosis of colorectal cancer, it does have value in prognosis (a level greater than 5 ng/mL is associated with poorer prognosis) and surveillance after surgical resection.23

Appropriate staging workup is particularly important in rectal cancers as it helps define the sequence of treatments, including which surgical approach is appropriate. Full colonoscopy is indicated to evaluate for synchronous cancers prior to further management. Synchronous second primary cancers are found in up to 5% of patients.24 Rigid sigmoidoscopy is used to determine the distance between the distal tumor margin and the top of the anorectal ring as well as the orientation of the tumor.

Computed tomography (CT) scans of the thorax, abdomen, and pelvis are routinely performed to evaluate for metastatic disease.25 In general, positron emission tomography (PET) scans are not routinely indicated in the staging of rectal cancer.26 Similarly, liver magnetic resonance imaging (MRI) can be used if there are equivocal results on CT scan.

Despite their use for distant disease, CT scans are not optimal for local evaluation of tumor depth, nodal invasion, and circumferential resection margin (CRM). The CRM is an important prognostic factor in rectal cancer as patients with a threatened CRM (tumor within 1 to 2 mm of the mesorectal fascia) are more likely to have local recurrence and should be considered for neoadjuvant chemoradiation, regardless of stage.27

For local disease evaluation and TNM staging (Table), transrectal ultrasound (TRUS) and rectal MRI are preferred over CT scan. TRUS helps distinguish cancers that penetrate the muscularis propria from those that involve only the mucosa or submucosa.28 It has been shown to be overall more accurate with regards to T staging, with sensitivity and specificity ranging from 88% to 98% for all T stages.29 However, TRUS has more interoperator variability.30,31 With regards to N staging accuracy, TRUS is similar to both CT and MRI.32

Rectal MRI can be performed with or without an endorectal coil. Some studies suggest that MRI has higher sensitivity for nodal staging than TRUS because MRI uses more than just size to determine if lymph nodes are involved (border irregularity, mixed signal).33 For predicting T stage, a meta-analysis showed that MRI has sensitivity and specificity of 87% and 75%, respectively.34 In a large meta-analysis of 90 studies comparing the 2 modalities, it was found that TRUS has higher specificity for T1 and T2 disease as well as higher sensitivity for T3 disease.32 However, another meta-analysis concluded that MRI was the best
modality for evaluating CRM. At present, either modality is acceptable for routine use.

**MANAGEMENT**

**CASE PATIENT CONTINUED**

The patient undergoes colonoscopy, which shows no evidence of synchronous cancers. CT scans of the thorax, abdomen, and pelvis as well as PET scan show no evidence of metastatic disease (Figure 1). TRUS confirms T3N1 disease (Figure 2).

- What is the current approach to treatment of locally advanced rectal cancer?

**NEOADJUVANT CHEMORADIOThERAPY**

The standard treatment for locally advanced rectal cancer is neoadjuvant chemoradiation with an infusional 5-fluorouracil backbone followed by surgical resection and adjuvant chemotherapy. Historically, the standard of care was adjuvant chemoradiotherapy until a randomized trial from Germany that assigned patients with T3/T4 or node-positive disease to neoadjuvant 5-fluorouracil with radiation versus adjuvant chemoradiotherapy showed improvement in the rate of sphincter-sparing surgery, local relapse, and toxicity. There was no difference in overall survival, however. This trial established a new standard of care that has subsequently been used throughout the United States and Europe. A similar trial, National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03, randomly assigned T3/T4 or node-positive patients to preoperative 5-fluorouracil with radiation versus adjuvant chemoradiotherapy. Though this trial closed early due to poor accrual, a statistically significant improvement in disease-free survival was seen in the neoadjuvant group and a trend towards improvement in overall survival.

### Table. TNM Staging for Locally Advanced Adenocarcinoma

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Regional lymph node (N)</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 Tumor invades submucosa</td>
<td>N0 No regional lymph node metastasis</td>
<td>I T1 N0</td>
</tr>
<tr>
<td>T2 Tumor invades muscularis propria</td>
<td>N1 Metastasis in 1–3 regional lymph nodes</td>
<td>IIA T3 N0</td>
</tr>
<tr>
<td>T3 Tumor invades through muscularis propria into peri-rectal tissue</td>
<td>N1a Metastasis in 1 regional lymph node</td>
<td>IIB T4a N0</td>
</tr>
<tr>
<td>T4a Tumor penetrates visceral peritoneum</td>
<td>N1b Metastasis in 2–3 regional lymph nodes</td>
<td>IIIA T1-T2 N1/N1c</td>
</tr>
<tr>
<td>T4b Tumor directly invades or is adherent to other organs or structures</td>
<td>N1c Tumor deposit(s) in the subserosa, mesentery, or perirectal tissue without regional node metastasis</td>
<td>T1 N2a</td>
</tr>
<tr>
<td>N2 Metastasis in 4 or more regional lymph nodes</td>
<td>N2a Metastasis in 4–6 regional lymph nodes</td>
<td>IIIB T3-T4a N1/N1c</td>
</tr>
<tr>
<td></td>
<td>N2b Metastasis in ≥7 regional lymph nodes</td>
<td>T2-T3 N2a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1-T2 N2b</td>
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<tr>
<td></td>
<td></td>
<td>IIIC T4a N2a</td>
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<td>T4b N1-N2</td>
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was observed as well.\textsuperscript{37} Interestingly, there was no difference in locoregional control between the groups. A Korean phase 3 trial randomly assigned the same population of patients (T3/T4 or node-positive) to preoperative capecitabine with radiation versus postoperative chemoradiation.\textsuperscript{38} However, all patients received an additional 4 cycles of postoperative capecitabine. There was no benefit with regards to survival or rate of local recurrence, but the preoperative group patients with low lying tumors did have an increase in sphincter-sparing operations. In this trial, preoperative chemoradiotherapy did not appear to increase the perioperative complication rate from surgical resection.

The large European Organisation for Research and Treatment of Cancer (EORTC) 22921 study evaluated both the role of preoperative chemotherapy with radiation as well as the role for adjuvant treatment. Patients with T3 or T4 disease were randomly assigned to preoperative radiation alone versus 5-fluorouracil with radiation and then to 4 cycles of postoperative 5-fluorouracil, using a 2 \times 2 factorial design.\textsuperscript{39,40} Improvement in disease-free survival was found if chemotherapy was given at some point during treatment, but there was no improvement in overall survival. In another study of patients with unresectable T4 or recurrent tumors, the combination of chemotherapy and radiation together was shown to improve overall survival compared to radiation alone.\textsuperscript{41} However, a meta-analysis of several studies comparing radiation alone to chemoradiotherapy demonstrated improvement in local control but no improvement in overall survival.\textsuperscript{42} Though no sustained benefit in overall survival has been established, neoadjuvant chemoradiotherapy remains the standard of care for T3, T4, and node-positive disease.

In the past, chemotherapy options were limited and infusional 5-fluorouracil has been the standard of care because of its tolerability. Bolus 5-fluorouracil with leucovorin has been evaluated,\textsuperscript{43} but is not routinely utilized given the additional toxicities associated with this regimen. Data from the adjuvant setting suggests that infusional 5-fluorouracil might be more effective with regards to local recurrence and overall survival compared to the bolus regimen.\textsuperscript{44} Capecitabine has been shown to be noninferior to infusional 5-fluorouracil in this setting.\textsuperscript{45,46} A retrospective trial has even shown improvement in pathologic complete response rate with capecitabine.\textsuperscript{45,47} This has led to capecitabine being used interchangeably with infusional 5-fluorouracil. However, more toxicity with capecitabine has been described as compared to 5-fluorouracil, including more hand/foot skin reaction, fatigue, and radiation dermatitis.\textsuperscript{48}

In an effort to improve local control, response rate, and overall survival, novel agents have been added to a 5-fluorouracil backbone. Because of its role in potentiating 5-fluorouracil in the metastatic
setting, leucovorin has been added to the chemoradiotherapy regimen. As there are no prospective, randomized trials, the benefit of adding leucovorin is unclear and it is not recommended as part of routine practice. Similarly, the addition of irinotecan in a phase 2 study did not show any significant benefit. Phase 2 trials have shown tolerability of bevacizumab, cetuximab, and panitumumab added to neoadjuvant chemoradiotherapy in locally advanced rectal cancer, but these results have not been validated in phase 3 trials and these agents are not part of current practice. The addition of oxaliplatin has been evaluated in several trials and has generally shown increased toxicity but no significant benefit. However, the German AIO randomly assigned patients with T3, T4, or node-positive rectal cancer to 5-fluorouracil with radiation with or without the addition of oxaliplatin, both as part of neoadjuvant treatment and as part of the adjuvant chemotherapy-alone regimen. The patients who received oxaliplatin had improvement in disease-free survival though the data are not yet mature regarding overall survival.

In addition to optimal selection of a chemotherapy backbone, another effort to tailor treatment regimens to specific patients has been underway. Pelvic radiation has long been part of the standard of care of locally advanced rectal cancer to decrease the risk of local recurrence. However, given the high rate of distant metastatic disease after treatment as well as toxicities from radiation, there has been interest in the earlier introduction of more intense systemic neoadjuvant chemotherapy without radiation in selected patients. In a pilot study, patients with T3 node-negative or node-positive rectal cancer were treated with 6 cycles of FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin). Adjuvant radiation was planned if there was stable or progressive disease seen during surgery, but all the patients had a response and did not require radiation. They had similar outcomes to historical controls. A multicenter phase 3 study is underway to further evaluate these promising results. However, this approach cannot yet be recommended in routine practice.

The type of radiation delivered has been studied in various trials. The established standard is to treat patients to 50.4 centigray (cGy) using 3-dimensional conformal radiation therapy. A boost to the tumor bed brings the radiation dose to 54 cGy. Short-course radiotherapy (5 days of 5 cGy) has been evaluated in T3 node-negative and node-positive rectal cancer. Patients were randomly assigned to standard chemoradiotherapy versus
short-course radiation followed by surgery and adjuvant chemotherapy. There was no significant difference between groups, though there was a trend towards increased local recurrence in the short-course radiotherapy group. In a similar study of T3 or T4 lesions, no significant difference was found between groups.\(^6\) In clinical practice, long-course radiotherapy remains the standard treatment. Despite many trials to delineate an improved outcome with decreased toxicity, for now the standard of care for T3/T4 or node-positive rectal cancers remains chemoradiotherapy with an infusional 5-fluorouracil backbone.

CASE CONTINUED

The patient receives neoadjuvant chemoradiation with infusional 5-fluorouracil and 54 cGy but is hesitant about proceeding with surgery because of the risk of complications and the possibility of a permanent colostomy.

SURGICAL RESECTION

The types of surgical resection for rectal cancer include the low anterior resection and the abdominoperineal resection. The former is sphincter sparing and is generally used for cancers in the middle to upper third of the rectum. Abdominoperineal resection are generally reserved for lower lying cancers and those in whom negative margins cannot be achieved with a sphincter-sparing procedure. In either case, a total mesorectal excision (excising a larger plane past the mesorectum) has been associated with significantly improved outcomes and is the preferred approach.\(^6\)

In general, it is advisable to wait between 4 and 6 weeks after the completion of chemoradiation to proceed with surgery to allow for maximum shrinkage of the tumor. Studies have been performed to evaluate longer and shorter wait times, but the optimal interval between completion of neoadjuvant conventional fractionated radiation therapy and surgery in rectal adenocarcinoma remains unknown.\(^6\)

CASE CONTINUED

The patient agrees to undergo surgery and has a low anterior resection, which she tolerates well. Pathology shows that her disease is down staged from a T3N1 to T2N1, with 1 lymph node positive out of 18 nodes examined. Tumor regression grade (TRG) is 1, indicating a moderate response.

ADJUVANT TREATMENT

TRG describes the degree of tumor regression after treatment. A 3-point TRG has been shown to be the most reproducible and to have prognostic value.\(^6\) At present, the post-surgical management strategy is not altered by factors like TRG.

In the United States, adjuvant chemotherapy is the standard of care for all patients with locally advanced rectal cancer who received neoadjuvant chemoradiotherapy.\(^2\) This standard has been extrapolated from studies showing the benefit of adjuvant therapy that were performed prior to the era of regular use of neoadjuvant therapy. However, trials have not definitively shown benefit of adjuvant therapy in patients who received neoadjuvant chemotherapy.

Prospective randomized studies have evaluated the role for adjuvant chemotherapy in patients who received neoadjuvant chemotherapy but have had conflicting results regarding which patients are likely to benefit. In the EORTC 22921 trial, patients who had received either radiation alone or neoadjuvant chemoradiation were randomly assigned to postoperative 5-fluorouracil with leucovorin or no adjuvant therapy.\(^3\) The initial results showed an improvement in local control with the addition of chemotherapy
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given before or after surgery. However, a recent update of EORTC 22921 suggests that there is no significant disease-free or overall survival benefit of adjuvant chemotherapy in patients who received preoperative radiotherapy or chemoradiotherapy. This finding has not yet changed clinical practice, likely because there was a significant lack of adherence to postoperative therapy; over half of the patients in the adjuvant chemotherapy groups did not receive the intended 4 cycles of treatment and 25% did not receive any adjuvant therapy.

Another prospective study from Italy randomly assigned patients who had received preoperative chemoradiotherapy to adjuvant bolus 5-fluorouracil and leucovorin versus observation and showed no advantage in disease-free or overall survival.65 Similarly, the Dutch PROCTOR/SCRIPT trials randomly assigned patients with stage II and III rectal cancers to postoperative 5-fluorouracil and leucovorin or capecitabine versus observation after having received neoadjuvant chemoradiotherapy. There was no difference in overall survival between groups.66 The UK Chronicle trial randomly assigned patients who had received neoadjuvant fluoropyrimidine therapy to adjuvant capecitabine with oxaliplatin versus observation. Though the trial was closed early secondary to poor accrual, there was a suggestion of improvement in disease-free survival for the treatment arm, but this was not statistically significant. There was no difference in overall survival.

Meta-analyses of the individual patients in these studies have concluded that fluoropyrimidine-based adjuvant therapy has not yet been shown to improve disease-free or overall survival.67,68 However, this treatment remains the standard of care and ongoing trials might definitively answer this question.66,69,70 At present, physicians should discuss the risks and benefits of adjuvant treatment with individual patients.

The choice of adjuvant regimen has also been evaluated. The phase 2 ADORE study randomly assigned rectal cancer patients with pathologic T3/T4 or node-positive disease to FOLFOX versus 5-fluorouracil and leucovorin and showed a benefit of FOLFOX with regards to disease-free survival.71 The overall survival data is still premature, but there is a suggestion of overall survival benefit with FOLFOX as well. Another study, the German AIO trial, randomly assigned patients with T3/T4 or node-positive disease at diagnosis to oxaliplatin as part of both neoadjuvant and adjuvant treatment, regardless of pathologic response. They found a disease-free survival benefit compared to 5-fluorouracil alone but no improvement in overall survival.39,58

**SURVEILLANCE AND LONG-TERM EFFECTS**

**CASE CONTINUED**

The patient receives adjuvant chemotherapy with FOLFOX for a total of 8 cycles. Though she has few symptoms during treatment, she develops numbness and tingling in her feet bilaterally after completion of chemotherapy.

- **What are the current recommendations regarding surveillance following treatment for locally advanced rectal cancer?**

In current standard practice, after the completion of treatment for locally advanced rectal cancer, patients should have a clinical encounter, including a careful history and physical exam, with their physician every 3 to 6 months for the first 3 years and every 6 months during years 4 and 5. A serum CEA level should be measured at each follow-up visit for the first 3 years. In addition, annual CT scans of the chest, abdomen, and pelvis for at
least 3 years should be obtained. In addition to the perioperative full colonoscopy to detect synchronous lesions, a repeat colonoscopy should be performed 1 year later to exclude new lesions. If this is normal, subsequent studies should be performed at intervals of 3 to 5 years depending on the results of the prior colonoscopy.

The purpose of intensive surveillance is to identify asymptomatic recurrence in patients who could then receive curative intent surgery. The recurrence risk is highest within 2 to 3 years after surgery and drops significantly after 5 years. The components of surveillance have been individually evaluated. History and physical examination have not been shown to contribute to early detection. Serial CEA measurements and routine CT were compared to minimal follow up in a large UK study and found to detect recurrent disease earlier and allow patients to go for curative surgery more often. However, there was no statistically significant difference in survival. The role of CEA monitoring is controversial. Though it is not sensitive or specific as a screening test, it can be correlated to disease burden and has prognostic value. CEA has been shown to detect disease earlier than other modalities, although it is questionable if that results in improved overall survival. A newly elevated CEA should be confirmed by retesting, as false positives are common. Though caution should be used with CEA testing, it is still recommended as part of routine practice.

Other tumor markers such as cancer antigen (CA) 19-9 and DR-70 have been evaluated but are not recommended for routine use in surveillance of colorectal cancers. Liver function tests and complete blood counts are also not routinely recommended as they are unlikely to help predict recurrence. Routine CT scans have been found to detect recurrent disease, especially in the liver, earlier than CT evaluation once symptoms arise and CT scan is therefore recommended annually. Several meta-analyses have shown a small overall survival benefit from intensive surveillance but have been limited by variation in the type of follow up utilized as well as the inclusion of stage I patients who likely do not need intensive follow up. Regular surveillance of patients with locally advanced rectal cancer after curative therapy is warranted.

In addition to surveillance for recurrent disease, patients should engage in a healthy lifestyle with regards to diet and exercise. Though this recommendation is based on observational studies, it has been adopted in the American Society of Clinical Oncology guidelines as part of secondary prevention of disease. Patients should be monitored for long-term toxicities of treatment. Quality of life often returns to normal about a year after treatment, but psychosocial issues stemming from treatment should be considered. Patients with a permanent ostomy can have issues with social relationships, sexual function, and depression. Medical problems after radiation and chemotherapy can include bowel and bladder dysfunction and neuropathy.

Though genetic syndromes have been established, the majority of colorectal cancers are sporadic. Careful family history should be updated regularly in order to evaluate for disorders like Lynch syndrome and familial adenomatous polyposis. Testing for microsatellite instability can be performed in at-risk patients, usually those younger than age 50 at diagnosis or who meet the Bethesda criteria, though some centers endorse universal testing.

**CONCLUSION**

The management of locally advanced rectal cancer continues to evolve. Careful staging helps
define those patients who will benefit from neoadjuvant therapy. This might continue to consist of chemoradiotherapy with a 5-fluorouracil backbone or may progress to exclude radiation for selected patients in the future based on the results of currently accruing studies. Surgical resection is the mainstay of therapy and should include attention to the CRM. Adjuvant therapy remains the established standard, although its utility is being evaluated in several ongoing trials. Finally, intense surveillance is appropriate for rectal cancer survivors, and particular attention should be paid to the unique set of psychosocial issues that arise from treatment.

BOARD REVIEW QUESTIONS

Test your knowledge of this topic.
Go to www.turner-white.com and select Oncology from the drop-down menu of specialties.

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